Self-reported restless legs syndrome and involuntary leg movements during sleep are associated with symptoms of attention deficit hyperactivity disorder

Didriksen, Maria; Thørner, Lise W.; Erikstrup, Christian; Pedersen, Ole B; Paarup, Helene M; Petersen, Mikkel; Hansen, Thomas F.; Banasik, Karina; Nielsen, Kaspar R; Hjalgrim, Henrik; Jennum, Poul J; Sørensen, Erik; Burgdorf, Kristoffer S; Ullum, Henrik

Published in:
Sleep Medicine

DOI:
10.1016/j.sleep.2019.01.039

Publication date:
2019

Document version
Peer reviewed version

Self-reported restless legs syndrome and involuntary leg movements during sleep are associated with symptoms of attention deficit hyperactivity disorder

Maria Didriksen[1], Lise W. Thørner[1], Christian Erikstrup[2], Ole B. Pedersen[3], Helene M. Paarup[4], Mikkel Petersen[2], Thomas F. Hansen[5], Karina Banasik[6], Kaspar R. Nielsen[7], Henrik Hjalgrim[8,9], Poul J. Jennum[10,11], Erik Sørensen[1], Kristoffer S. Burgdorf[1], Henrik Ullum[1]

[1]Department of Clinical Immunology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

[2]Department of Clinical Immunology, Aarhus University Hospital, Aarhus, Denmark

[3]Department of Clinical Immunology, Naestved Sygehus, Naestved, Denmark

[4]Department of Clinical Immunology, Odense University Hospital, Odense, Denmark.

[5]Danish Headache Center, Department of Neurology, Glostrup Research Institute, Rigshospitalet Glostrup, Glostrup, Denmark

[6]The Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

[7]Department of Clinical Immunology, Aalborg University Hospital, Aalborg, Denmark

[8]Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark

[9]Department of Hematology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark.

[10]Department of Clinical Neurophysiology, Danish Center for Sleep Medicine, Copenhagen University Hospital, Rigshospitalet, Glostrup, Denmark.

[11]Faculty of Health, University of Copenhagen, Copenhagen, Denmark

Corresponding author: Maria Didriksen. Department of Clinical Immunology, Rigshospitalet, Copenhagen, Denmark. Contact information: maria.didriksen@regionh.dk

The institution where the work was performed: Department of Clinical Immunology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

Highlights

- Individuals with restless leg syndrome (RLS) have an increased risk of attention-deficit-hyperactivity-disorder (ADHD)
- RLS sufferers with involuntary leg movements during sleep are more prone to experience ADHD symptoms compared to sufferers without ILMS
- Quality of sleep explains the association only to a limited extent
- RLS and ADHD may be comorbid disorders

Abstract

Background: Restless legs syndrome (RLS) and attention-deficit hyperactivity disorder (ADHD) are disorders with virtually unknown etiologies. Several studies suggest that these disorders are comorbid. However, previous findings may have been influenced by study participants undergoing medical treatments. Thus, the association between RLS and ADHD needs to be investigated in a large population of individuals, not in continuous medical treatment.

Materials and Methods: This was a cross-sectional study of 25,336 participants enrolled in the Danish Blood Donor Study from May 1, 2015, to February 1, 2017. Study participants completed the Cambridge-Hopkins RLS questionnaire, experienced involuntary leg movements during sleep (ILMS), completed the Adult ADHD Self-Report Scale v.1.1 (ASRS), and provided sex, age, body mass index, smoking status, alcohol consumption, whole blood donation history, and self-appraised quality of sleep. Associations between RLS and ADHD symptoms, including the inattention and hyperactivity-impulsivity subtypes, were examined using multivariate linear- and logistic regression analyses.

Results: Of the 25,336 participants with complete data, 1,322 (5.2%) were classified with RLS, and 653 (2.6%) experienced ADHD symptoms. RLS sufferers were more prone to classify with ADHD according to the full ASRS (OR=3.57, 95% CI: 3.14-4.0), and they were also more likely to experience ADHD-subtype symptoms (inattention, OR=1.66, 95% CI: 1.43-1.90; hyperactivity-impulsivity, OR=1.90, 95% CI: 1.66-2.14). Finally, RLS sufferers with ILMS had increased odds for ADHD symptoms compared with RLS sufferers without ILMS (OR=2.15, 95% CI: 1.30-3.55). This was also observed for the hyperactivity-impulsivity subtype (OR=5.57, 95% CI: 2.14-14.5).

Conclusions: RLS and ADHD are associated and may be comorbid disorders.

Keywords: Restless Legs Syndrome; Attention-deficit-hyperactivity-disorder; comorbidities; sleep; neurology; The Danish Blood Donor Study

Previous studies have indicated that there is an association between restless legs syndrome (RLS) and attention-deficit hyperactivity disorder (ADHD), which are neuropsychiatric disorders with etiologies that are still not fully understood

We have shown that 7.2% of women and 4.5% of men participating in the Danish Blood Donor study [1, 2] suffer from RLS [3]. RLS is a neurological sensorimotor disorder including uncomfortable or painful sensations in the extremities, predominantly in the legs. The symptoms have a strong circadian pattern as they become worse at night, which means that most RLS sufferers experience severe sleep disturbance [4, 5]. Many individuals with RLS experience involuntary leg movements during sleep (ILMS), which reduces the quality of sleep even more. Previous studies have reported that RLS sufferers are more prone to experience inhibited cognitive functioning and psychosocial distress, including problems with social activities, family life, and occupational life due to fatigue following disruptions in sleep [6, 7]. Moreover, we showed that suffering from RLS is associated with an increased risk of depression [8], migraine [9], and low health-related quality of life [8]. Thus, it is evident that RLS is a disorder with severe consequences for the affected. In a previous study, we found that 2.6% of participants in the Danish Blood Donor Study classified with ADHD [10]. ADHD is characterized by age-inappropriate levels of inattention, impulsivity and/or hyperactivity with symptom onset in childhood [11]; however, it has become established knowledge that ADHD symptoms persist into adulthood [10, 12, 13]. Like RLS, ADHD has been associated with other neuropsychiatric disorders such as depression [13], migraine [14], and reduced health-related quality of life [15]. Moreover, it has been found that individuals with ADHD have a higher mortality rate compared to individuals without ADHD and that a large part of this higher mortality

was caused by death from accidents [16]. Thus, ADHD is – like RLS – associated with a high risk of severely detrimental comorbidities.

The previously suggested association between RLS and ADHD may be caused by the fact that both RLS and ADHD have been linked with poor quality of sleep and with iron deficiency. Cortese et al. (2008) suggested that the disorders may be related by iron deficiency, as this state affects the function of catecholamines, in particularly the dopaminergic system resulting in reduced levels of dopamine and serotonin [11]. Moreover, it is well known that disorders that cause sleep disturbances can result in - or contribute to- behavioral problems with mood and inattention [17]. Thus, it is possible that RLS can cause ADHD or ADHD-like symptoms. Furthermore, a recently published case-control study showed that a high proportion of children with ADHD suffer from a periodic limb movement disorder (10.2%), while no children in the control group suffered from this disorder [18]. This finding suggests that an association between ADHD and RLS may vary according to the sufferers' experience with ILMS.

Studies that examined the RLS-ADHD association included small numbers of participants who may have been undergoing medical treatments affecting either or both disorders, which could have had an impact on the findings. Blood donor populations are suitable for studying this association because the individuals are required to be generally healthy, have a normal iron level, and not to be on any medical treatment to be eligible as donors. Therefore, this study aims to investigate the association of RLS with ADHD in a large population of Danish blood donors while taking their quality of sleep and experience of ILMS into account.

1. Methods

1.1 Data

Data for this study were collected from the Danish Blood Donor Study (DBDS) (www.dbds.dk), an ongoing national cohort of Danish blood donors, which is described in detail elsewhere [1, 2]. Briefly, the DBDS utilizes the infrastructure in the Danish blood banks to collect data for a range of general health research purposes. Individuals who have donated at least two times in a Danish blood bank were asked to participate in the study. Upon inclusion, each participant filled out a comprehensive health-related electronic questionnaire. The questionnaire provided information on RLS, ADHD, and covariates. Moreover, the participants gave permission for their questionnaire data to be linked with data from the Danish population registers, from which we retrieved information on sociodemographic characteristics.

1.1.1 A generally healthy population

To be eligible to donate blood an individual is required to be healthy and not undergoing any medical treatment, such as dopaminergics, gabapentin or opioids which are used to treat RLS, or medications based on dextroamphetamine, methylphenidate, Lisdexamfetamine, Atomoxetine, Clonidine, and Guanfacine which are used to treat ADHD. Participants included in this study did not suffer from other neurological or psychiatric disorders for which they received medical treatment. Before donating blood, Danish blood donors are asked several screening questions designed to assess if they are entirely well. This is done both through a personal interview and by using a generic health questionnaire that assesses a donor's mental and physical health. Among other things, the donors are asked if they have taken any medications, or if they have been sick since their last donation. These screening questions assure that the donors are generally healthy at the time of each donation, and thus also upon inclusion into this study. Finally, upon each donation to a Danish

blood bank, donors' hemoglobin levels were measured. To be eligible for donation, each donor is required to have sufficient hemoglobin levels for men and women ((hemoglobin levels>7.8 mmol/L (12.5 g/dL) and 8.4 mmol/L (13.5 g/dL), respectively).

1.1.2 Restless legs syndrome (RLS)

RLS was assessed using the 10 item Cambridge-Hopkins RLS questionnaire (CH-RLSq), which is the only tool validated in a population of blood donors [19] (diagnostic sensitivity 87.2% and specificity 94%) [20], and recommended as one of the most accurate scales for identifying individuals suffering from RLS [21]. The CH-RLSq was translated from English to Danish using the back-translation method, which is described in detail elsewhere [8]. Participants who presented with RLS symptoms were asked to rate their symptoms' severity and frequency, ranging from "not uncomfortable" to "extremely uncomfortable" (4-point Likert scale) and from "one day a month" to "every day" (6-point Likert scale), respectively. Participants experiencing RLS symptoms were also asked if they have experienced involuntary leg movements during sleep or been told by their bed partner that their legs move during sleep (yes/no).

1.1.3 Attention deficit hyperactivity disorder (ADHD)

The presence of ADHD symptoms was assessed using the Adult ADHD Self-Report Scale v.1.1 (ASRS) [22], which has been validated in several population samples [23-26]. This version was used because it is the National clinical standard for assessing ADHD symptoms in Denmark. The translation of the ASRS from English to Danish is described elsewhere [27]. The ASRS has been reported to have good reliability and diagnostic utility among adults with a sensitivity of 0.92, a specificity of 0.69, and positive and negative predictive values of 0.48 and 0.97, respectively[28]. Similar psychometric properties were reported among Scandinavian adolescents[26]

The ASRS comprises 18 questions, which were designed according to diagnostic criteria for ADHD from the *Diagnostic and statistical manual of mental disorders fourth edition*. Each question in the

ASRS assesses the presence of an ADHD symptom using a 5-point Likert scale, by which the participants indicate how often they experience the symptom in question; ranging from “never” (0) to “very often” (4). In this study, a participant was classified with ADHD symptoms if they had a score of 37 or above on the full ASRS scale, which is a validated cut-off used in previous studies [24]. We also considered subtypes of ADHD using different blocks of questions from the ASRS: 1) the 6-question screening version, which comprises the first six questions on the scale (ADHD symptoms are considered present with a score above or equal to 14). The six screening questions assess the presence of the six ADHD symptoms regarded as the most pronounced. This part of the scale is often used by general physicians to screen for ADHD-symptoms before visitation to psychiatrists. 2) The inattentive ADHD subtype, which was assessed using questions 1 through 4 and 7 through 11 (inattentive symptoms are considered present with a score equal to or above 24). 3) The hyperactivity-impulsivity ADHD subtype was assessed using questions 5 through 6 and 12 through 18 (hyperactivity-impulsivity symptoms are considered present with a score equal to or above 24) [24].

1.1.4 Covariates

The electronic DBDS questionnaire provided information on smoking status (yes/no), body mass index (BMI), alcohol consumption, and quality of sleep. Participants were asked how often they experienced trouble sleeping at night during the past two weeks prior to inclusion in this study. Quality of sleep was dichotomized as poor quality versus good quality. Participants were classified with a poor quality of sleep if they reported trouble sleeping “more than half the time” for the two weeks prior to inclusion into this study or more frequently than that. Furthermore, the following data were collected from the national register: information on sociodemographic characteristics (sex and age) and donation frequency three years before inclusion into the study, which we have

previously reported to be the strongest predictor of iron deficiency among Danish blood donors [29]. Linking of individual-level data from the registers and the blood banks with data from the questionnaire had high validity, due to the use of unique Danish Civil Registration Numbers [30].

1.2 Ethics statement

Oral and written informed consent was obtained from all participants. The study was approved by The Scientific Ethical Committee of Central Denmark (M-20090237). Additionally, the research database has been approved by the Danish Data Protection Agency (2007-58-0015).

1.3 Statistical analyses

Statistical analyses were conducted using Stata/SE 14.0, StataCorp, College Station, TX. Continuous variables were described with means and standard deviations (SD), while binary variables were described in percentages. Frequent alcohol consumption was defined as alcohol consumption "several times a week" or "every day." Statistically significant differences were investigated by t-tests for normally distributed data and by chi^2-tests for dichotomous data. Before examining statistically significant differences in score, age was log-transformed to obtain a normal distribution of the scale. Univariate and multivariate linear regression analyses were conducted to investigate the correlation between RLS status and ASRS score. Univariate and multivariate logistic regression analyses were applied to assess the probability of experiencing ADHD symptoms (herein the different ADHD subtypes) among participants with RLS compared to participants without. Similar analyses were used to examine the likelihood of ADHD symptoms in RLS sufferers with and without ILMS. Sex, age, BMI, smoking, frequent alcohol consumption, and donation frequency for the past three years were all considered possible covariates of the associations [3, 29, 31, 32] and were included in all multivariate regression analyses as binary variables, except for age and BMI, which were included as continuous variables. Quality of sleep was entered as a covariate in part of the analyses (as indicated in Tables 2 and 3).

2. Results

2.1 Characteristics of the study population

Out of 25,336 participants with complete data, 1,322 (5.2%) were classified with RLS of whom more were women (57.6%) than men. Furthermore, 653 (2.6%) were classified with ADHD, while 525 (2.1%) had a score of 14 or above on the screening part of the scale. We found that 179 (0.7%) participants classified with the inattentive ADHD subtype, whereas 143 (0.6%) participants classified with the hyperactivity-impulsivity ADHD subtype. Initially, 27,315 individuals were included in this study between May 2015 and February 2017. Of these, 891 and 909 were excluded due to missing data on the CH-RLSq and the ASRS, respectively. We also excluded 124 participants who had failed to answer at least one of the questions regarding BMI, smoking status, and alcohol consumption. Fifty participants were excluded due to missing data on quality of sleep, and finally, 3 RLS sufferers were excluded due to missing data on ILMS.

We found that 295 (22.3%) of the RLS cases reported experiencing ILMS, and that poor quality of sleep was more prevalent among participants with RLS than without RLS. ADHD subtypes were more prevalent among RLS cases (Table 1). We also observed that poor quality of sleep was more prevalent among RLS sufferers with ADHD symptoms than among RLS sufferers without ADHD symptoms (26.7% versus 9.1%; $P<0.001$).

Table 1. Demographic and clinical features of the study population

Characteristics	RLS N=1,322	No RLS symptoms N=24,014	P *
Involuntary leg movements during sleep (%)	22.3	-	-
Female sex (%)	57.6	45.0	<.001
Age (mean ±SD)	42.2 (12.3)	41.3 (12.7)	0.006
Body mass index (Mean ±SD)	25.8 (4.2)	25.7 (4.1)	0.419
Smoker (%)	15.5	13.0	0.007
Frequent alcohol consumption (%)	38.3	35.5	0.042
Whole blood donation frequency for the past three years (mean ±SD)	5.2 (2.5)	5.4 (2.6)	0.004
Poor quality of sleep (%)	10.1	4.6	<.001
ADHD symptoms			
ASRS score (Mean ±SD)	23.0 (8.3)	19.4 (7.8)	<.001
Full ASRS scale (score>36 on all 18 questions) (%)	5.7	2.4	<.001
Screening version of ASRS (score>6 on questions 1-6) (%)	4.2	2.0	<.001
Inattentive subtype (score ≥24 on questions 1-4 and 7-11) (%)	1.4	0.7	0.003
Hyperactivity-impulsivity subtype (score ≥24 on questions 5-6 and 12-18) (%)	1.4	0.5	<.001

*Body mass index was transformed using square root to obtain normal distribution before examining significant differences between RLS and non-RLS sufferers.

2.2 Restless legs syndrome (RLS) and attention-deficit hyperactivity disorder (ADHD)

Multivariate linear regression analyses showed that the ASRS score was positively correlated with RLS (P<0.001) (Table 2). Moreover, we found that RLS sufferers had increased odds for ADHD compared to controls. This was observed both when ADHD was classified according to the full ASRS scale and when classified according to the screening version of the scale. Also, RLS sufferers

had increased odds for being classified with the inattentive ADHD subtype and with the hyperactivity-impulsivity ADHD subtype. The highest odds ratio (OR) for RLS sufferers compared to controls was observed for the hyperactivity-impulsivity ADHD subtype (OR=4.28, P<0.001) (Table 3).

We found higher odds for ADHD and subtypes among RLS sufferers who reported experiencing ILMS compared to RLS cases who reported no experience of ILMS, as well as compared to controls (Table 4). When examining each question on the ASRS scale, we found that RLS sufferers had a statistically significantly higher mean score on each of the 18 questions compared to non-RLS sufferers and that the associations observed in this study were not caused by any one specific question on the scale.

When the quality of sleep was included in the statistical models as a covariate, the risk estimates were marginally attenuated (both the linear regression models and the logistic regression models). The fit of all models increased as indicated by R-squared (Tables 2, 3, and 4).

Table 2. Univariate and multivariate linear regression analyses with Restless Legs Syndrome (RLS) as the independent variable and continuous ASRS score as the dependent variable

Non-RLS cases, n=24,014 RLS cases, n=1,322	**Univariable analyses** Coef. (95 % CI)	P	**Model 1*** Coef. (95 % CI)	P	**Model 2**** Coef. (95 % CI)	P
Comparison groups: RLS vs. no RLS						
Full ASRS scale (score on all 18 questions)	3.56 (3.13-3.99)	<.001	3.57 (3.14-4.00)	<.001	3.26 (2.84-3.68)	<.001
The full scale divided into the ADHD subtypes						
Inattentive subtype (score on questions 1-4 and 7-11)	1.61 (1.37-1.86)	<.001	1.66 (1.43-1.90)	<.001	1.52 (1.28-1.75)	<.001
Hyperactivity-impulsivity subtype (score on questions 5-6 and 12-18)	1.95 (1.70-2.19)	<.001	1.90 (1.66-2.14)	<.001	1.74 (1.50-1.98)	<.001

*Adjusted for sex, age, body mass index (BMI), alcohol consumption, smoking status, and whole blood donation frequency for the past three years
**Adjusted for sex, age, BMI, alcohol consumption, smoking status, and whole blood donation frequency for the past three years and quality of sleep (poor/good)

Table 3. Univariate and multivariate logistic regression analyses with restless legs syndrome (RLS) as the independent variable and ADHD symptoms as the dependent variable

Non-RLS cases, n=24,014 RLS cases, n=1,322	**Univariable analyses** OR (95 % CI)	P	**Model 1*** OR (95 % CI)	P	**Model 2**** OR (95 % CI)	P
Comparison groups: RLS vs. no RLS						
ADHD symptoms						
Full ASRS scale (score≥37 on all 18 questions)	2.44 (1.90-3.12)	<.001	2.62 (2.04-3.37)	<.001	2.34 (1.81-3.03)	<.001
Screening version of ASRS (score≥14 on the first 6 questions)	2.22 (1.67-2.95)	<.001	2.51 (1.88-3.35)	<.001	2.27 (1.69-3.04)	<.001
The full scale divided into the ADHD subtypes						
Inattentive subtype (score ≥24 on questions 1-4 and 7-11)	2.05 (1.25-3.34)	0.004	2.25 (1.37-3.68)	0.001	1.91 (1.15-3.15)	0.012
Hyperactivity-impulsivity subtype (score ≥24 on questions 5-6 and 12-18)	2.81 (1.73-4.57)	<.001	4.28 (2.55-7.18)	<.001	3.46 (2.04-5.89)	<.001

*Adjusted for sex, age, body mass index, alcohol consumption, smoking status, and whole blood donation frequency for the past three years

**Adjusted for sex, age, body mass index, alcohol consumption, smoking status, and whole blood donation frequency for the past three years and quality of sleep (poor/good)

Table 4. Univariate and multivariate logistic regression analyses with restless legs syndrome (RLS) as the independent variable and ADHD symptoms as the dependent variable

Non-RLS cases, n=24,109 RLS cases with ILMS, n=295	**Univariable analyses** OR (95 % CI)	P	**Model 1*** OR (95 % CI)	P	**Model 2**** OR (95 % CI)	P
Comparison groups: RLS cases with involuntary leg movements during sleep (ILMS) vs. RLS cases without ILMS (N=295/1,027)						
ADHD symptoms						
Full ASRS scale (score≥37)	1.91 (1.36-	<.00	2.15 (1.30-	0.00	2.04 (1.22-	0.00

	2.68)	1	3.55)	3	3.41)	7
Screening version of ASRS (score≥14)	2.36 (1.35-4.09)	0.002	2.12 (1.21-3.74)	0.009	2.00 (1.13-3.56)	0.018
The full scale divided into the ADHD subtypes						
Inattentive subtype (score ≥24 on questions 1-4 and 7-11)	2.83 (1.11-7.25)	0.030	2.54 (0.97-6.68)	0.058	2.17 (0.80-5.88)	0.126
Hyperactivity-impulsivity subtype (score ≥24 on questions 5-6 and 12-18)	6.18 (2.41-15.84)	<.001	5.57 (2.14-14.5)	<.001	5.24 (1.98-13.9)	0.001
Comparison groups: RLS cases with involuntary leg movements during sleep (ILMS) vs. non-RLS cases (N=295/24,014)						
ADHD symptoms						
Full ASRS scale (score≥37)	4.25 (2.86-6.33)	<.001	4.33 (2.88-6.51)	<.001	3.69 (2.42-5.61)	<.001
Screening version of ASRS (score≥14)	4.05 (2.60-6.31)	<.001	4.24 (2.69-6.69)	<.001	3.62 (2.26-5.78)	<.001
The full scale divided into the ADHD subtypes						
Inattentive subtype (score ≥24 on questions 1-4 and 7-11)	4.13 (2.01-8.48)	<.001	4.28 (2.07-8.86)	<.001	3.42 (1.63-7.20)	<.01
Hyperactivity-impulsivity subtype (score ≥24 on questions 5-6 and 12-18)	8.17 (4.47-14.95)	<.001	8.09 (4.39-14.91)	<.001	6.61 (3.54-12.37)	<.001

*Adjusted for sex, age, body mass index, alcohol consumption, smoking status, and whole blood donation frequency for the past three years
**Adjusted for sex, age, body mass index, alcohol consumption, smoking status, and whole blood donation frequency for the past three years and quality of sleep (poor/good)

3. Discussion

This study confirms previous findings of an association between RLS and ADHD as our results showed a strong association between RLS and ADHD in a large population of individuals who were

not undergoing chronic medical treatment. Based on our study, we found that participants experiencing RLS symptoms were more likely to report ADHD symptoms and to experience ADHD subtypes' symptoms (the inattention subtype and the hyperactivity-impulsivity subtype). The OR for ADHD subtypes among RLS sufferers compared to non-sufferers was highest for the hyperactivity-impulsivity subtype.

Previous studies have suggested that the association between RLS and ADHD is mediated by the quality of sleep. This is based on the knowledge of poor quality of sleep being the primary comorbidity of RLS and that sleep disturbance causes problems with mood, attention, and hyperactivity, all of which are symptoms observed in ADHD sufferers. If this were the case, it is possible that ADHD-like symptoms will be reduced by treating the causative sleep disorder. However, the present results indicate that poor quality of sleep only mediates the association between RLS and ADHD to some extent as the OR's were marginally attenuated, but remained statistically significant when information on quality of sleep was introduced into the logistic regression analyses as a covariate. Thus, as stated in the introduction, there may be symptom overlap between RLS and ADHD. Another reason to consider this is that it is an intrinsic feature of the RLS disorder that sufferers feel an urge to move to relieve uncomfortable sensations in their legs and therefore they might not be able to do sedentary activities for longer periods; this might mimic the ADHD symptoms of inattention and hyperactivity.

Previous studies have shown an association between maternal RLS and increased prevalence of ADHD in offspring [34], which emphasizes the probability of a shared pathophysiological mechanism between the disorders. A potentially shared mechanism could be dopaminergic dysfunction [17], leading to the widely discussed iron hypothesis: having low iron stores has numerous times been linked with the development of both RLS and ADHD symptoms [11, 35]. As the present study comprised blood donors, which is a population at increased risk of having low

iron stores[29], it is especially relevant to discuss the potential role of iron in both the disorders as well as in the observed associations. When dealing with blood donors, one should bear in mind that they are screened for iron deficiency by means of hemoglobin measurements to be eligible for blood donation. Thus, it is possible that some participants in this study had a normal hemoglobin level, but a low ferritin level. Low iron stores in the brain, which causes synaptic dysfunction affecting dopaminergic transmission may be the common pathway between RLS and the phenotypic spectrum of ADHD and subtypes [36, 37]. Cortese et al. (2008) hypothesized that the catecholaminergic systems could be impacted differently by low iron stores making RLS and ADHD two different phenotypic expressions of iron deficiency [11]. Thus, RLS and ADHD may be part of a symptom complex, in which a dopaminergic deficiency, which results from iron deficiency, plays a role. However, this mechanism is complex and needs thorough investigation, as a randomized controlled trial (RCT) showed that treatment with L-dopa only improved the RLS-related symptoms and not the symptoms related to ADHD in children suffering from both disorders [38]. In line with this, another RCT showed that the majority of children with ADHD experienced prolonged sleep latency and non-specific leg movements during sleep and that these leg movements did not get better when treated with L-dopa [39].

An explanation was also put forward by Hvolby et al. (2015), who published a possible conceptual model of the interaction between the two disorders. This model stated that RLS-related sleep problems may cause or simulate ADHD symptoms and that the ADHD symptoms may interact with sleep problems causing reciprocal maintenance or worsening of the converse condition. Finally, the study suggested that ADHD and sleep problems could have a common underlying neurological etiology [40]. Before this conceptual model was published, Konofal et al. (2010) suggested that the presence of RLS should be systematically investigated in patients with ADHD symptoms [17]. This is emphasized further by the fact that ADHD patients often experience problems with learning

due to a poor ability to concentrate, which is a state that is worsened or provoked by sleep issues. The present study supports these suggestions, and the present findings combined with these previous reports, indicate that treatment of RLS and related sleep problems in individuals with ADHD may result in a reduction of ADHD symptoms.

The main strength of the present study was the size of the cohort, the data available, and the fact that all analyses were adjusted for relevant sociodemographic-, lifestyle-, and donation factors. Even so, our findings may be affected by "the internal healthy donor effect," which describes the fact that blood donors represent a healthy subgroup of the general population, and that frequently-donating individuals are generally healthier than infrequently-donating donors [41]. Therefore, it is possible that our study population only comprises individuals with mild versions of the disorders, as it is likely that people with severe RLS or ADHD symptoms stop donating blood, and that the most severe cases never even become blood donors due to the selection of generally healthy individuals. This is supported by the fact that individuals being treated with RLS or ADHD medications are not allowed to be blood donors. Thus, the internal healthy donor effect could have masked negative effects of donation-induced iron deficiency on both RLS and ADHD. Moreover, as noted previously, the healthy donor effect also means that the associations observed in this study cannot be attributed to differential morbidities, especially ones requiring medical treatment. Furthermore, there may also be a bias related to the personality type of individuals who volunteer to donate blood.

It is not possible for us to draw conclusions about directionality or causality of the observed associations as the collected data were cross-sectional. This also means that we were not able to draw conclusions regarding the long-term effects of RLS. Another point worth mentioning is that misclassification bias is possible in this study due to the self-report nature of the questionnaire data. However, because we used validated questions and scoring schemes, it is likely that any

misclassification would be random and not bias the results. Furthermore, the occurrence of ILMS in RLS sufferers observed in this study may be underestimated as the method used for assessing the experience of ILMS is susceptible to recall bias. This is emphasized by other studies reporting periodic leg movements in sleep (PLMS) in up to 80% of RLS sufferers [42]. A self-reported measure of ILMS is non-specific; from this measure we cannot know anything about the nature of the movements, such as their periodicity. Further emphasizing the unspecific nature of the leg movement data collected in this study, a study of a population of patients undergoing evaluation for obstructive sleep apnea without RLS, noted that self-reported symptoms of leg jerking during sleep was a poor predictor of PLMS indices identified through objective polysomnography (PSG)[2]. Therefore, it would have been optimal had we used an objective method of measurement such as an electromyography or actigraphy examination or if we had asked about ILM during wakefulness instead of during sleep. Due to these concerns, it is plausible that individuals who reported an experience of ILMS in this study are the ones who were most bothered by such. It is also worth noting that, because we found a statistically significant association between RLS and ADHD when comparing RLS sufferers with and without the self-reported ILMS, it is likely that the true association is even stronger with higher risk estimates, as our control population may comprise RLS sufferers with ILMS, however, plausibly less severe ones.

4. Conclusions

This study showed evidence that RLS sufferers are more prone to experience ADHD symptoms and subtypes symptoms of ADHD compared to non-sufferers. Moreover, we found that RLS sufferers with ILMS had a further increased risk of reporting ADHD, in particular, the hyperactivity subtype compared to RLS sufferers without ILMS. In conclusion, the present findings demonstrate that RLS and ADHD are associated disorders in a large population that is not affected by continuous medical treatment. Whether the disorders are comorbid with a shared etiology or pathophysiology or if they

are merely part of the same symptomatic spectrum- or both- warrants further investigation. This could entail an investigation of shared genetic components between the two disorders, as well as an examination of brain iron levels in both RLS and ADHD sufferers. Furthermore, it would be highly relevant to look more into objective observations of sleep patterns among such patients, for example by applying actigraphy measurements.

5. Funding

This study was supported with grants from *The Danish Council for Independent Research - Medical Sciences* (09-069412), *The Danish Administrative Regions* (02/2611), *The Danish Blood Donor Research Foundation, The Danish Bio- and Genome bank,* and *The Brothers Hartmann Foundation* (A29659). The funders had no role in study design, data collection, and analysis, the decision to publish, or in preparation of the manuscript. Moreover, the work was supported by the Novo Nordisk Foundation (grant NNF14CC0001 and NNF17OC0027594).

6. Author contributions

Henrik Ullum (HU), Erik Sørensen (ES), Christian Erikstrup (CE), Ole B. Pedersen (OBP), Lise W. Thørner (LWT), Kristoffer S. Burgdorf (KSB), Helene M. Paarup (HMP), Mikkel Petersen (MP), Thomas F. Hansen (TFH), Karina Banasik (KB), Kaspar R. Nielsen (KRN), and Henrik Hjalgrim (HH): Collecting data and creating study platform. HU, ES, CE, OBP, LWT, KSB, HMP, MP, TFH, KB, KRN, HH, and Maria Didriksen (MD): Planning study design. MD: Statistical analyses, interpretation of results and completion of the first manuscript draft. HU, ES, CE, OBP, LWT, KSB, HMP, MP, TFH, KB, KRN, HH: Interpretation of analyses and revision of the first manuscript draft.

7. Conflict of interest

The authors have no conflict of interest to declare.

8. Acknowledgments

We wish to express a special thanks to the personnel in the Danish blood banks who made sure to include blood donors into the DBDS making this research possible. We also wish to thank the financial funders of the present project: *The Danish Council for Independent Research - Medical Sciences* (09-069412), *The Danish Administrative Regions* (02/2611), *The Danish Blood Donor Research Foundation, The Danish Bio- and Genome bank,* and *The Brothers Hartmann Foundation* (A29659). The funders had no role in study design, data collection, and analysis, the decision to publish, or in preparation of the manuscript. Moreover, the work was supported by the Novo Nordisk Foundation (grant NNF14CC0001 and NNF17OC0027594). Finally, we wish to acknowledge Professor Richard Allen, Johns Hopkins School of Medicine, Baltimore, US and Dr. Brendan Burchell, University of Cambridge, Cambridge, UK for advice on identifying individuals with RLS.

References

1. Pedersen, O.B., et al., *The Danish Blood Donor Study: a large, prospective cohort and biobank for medical research.* Vox Sang, 2012. **102**(3): p. 271.
2. Burgdorf, K.S., et al., *Digital questionnaire platform in the Danish Blood Donor Study.* Comput Methods Programs Biomed, 2016. **135**: p. 101-4.
3. Didriksen, M., et al., *Prevalence of restless legs syndrome and associated factors in an otherwise healthy population: results from the Danish Blood Donor Study.* Sleep Medicine, 2017. **36**: p. 55-61.
4. Winkelman, J.W., et al., *Polysomnographic and health-related quality of life correlates of restless legs syndrome in the Sleep Heart Health Study.* Sleep, 2009. **32**(6): p. 772-8.
5. Cotter, P.E. and S.T. O'Keeffe, *Restless leg syndrome: is it a real problem?* Ther Clin Risk Manag, 2006. **2**(4): p. 465-75.
6. *National Heart, Lung, and Blood Institute Working Group on Restless Legs Syndrome.* Am Fam Physician, 2000. **62**(1): p. 108-14.
7. Atkinson, M.J., et al., *Validation of the Restless Legs Syndrome Quality of Life Instrument (RLS-QLI): findings of a consortium of national experts and the RLS Foundation.* Qual Life Res, 2004. **13**(3): p. 679-93.
8. Didriksen, M.A., P. R; Burchell, B; Thørner W., L; Rigas S., A; Di Angelantonio, E; Nielsen H, M; Jennum, P.,J; Werge, T; Eikstrup, C; Pedersen, B.O; Nielsen, K; Bruun,

T.,M; Burgdorf S.K; Sørensen E., Ullum, H, *Restless legs syndrome is associated with major comorbidities in a population of Danish blood donors.* Sleep Medicine, 2018.
9. Didriksen, M. et al., *Restless legs syndrome is associated with increased risk of migraine.* Cephalalgia Reports, 2018. **1**: p. 2515816318780743.
10. Hoeffding LK, N.M., Nissen J, Didriksen M, Thomas Werge, Trine Schow, Christian Erikstrup, Ole Birger Pedersen, Henrik Hjalgrim, Jens RM Jepsen, Henrik Ullum, Kristoffer Burgdorf, *Symptoms of ADHD are highly common in undiagnosed adults – A cross-sectional study in a large population of Danes.* Journal of Psychiatry and Behavioral Sciences, 2018. **1:1004**.
11. Cortese, S., et al., *Attention-deficit/hyperactivity disorder, Tourette's syndrome, and restless legs syndrome: the iron hypothesis.* Med Hypotheses, 2008. **70**(6): p. 1128-32.
12. Asherson, P., et al., *Adult attention-deficit hyperactivity disorder: key conceptual issues.* Lancet Psychiatry, 2016. **3**(6): p. 568-78.
13. Pehlivanidis, A., et al., *Comorbid attention-deficit/hyperactivity disorder in adult psychiatric outpatients with depressive or anxiety disorders.* Int J Psychiatry Clin Pract, 2014. **18**(4): p. 265-71.
14. Fasmer, O.B., et al., *Adult attention deficit hyperactivity disorder is associated with migraine headaches.* Eur Arch Psychiatry Clin Neurosci, 2011. **261**(8): p. 595-602.
15. Lin, Y.J., et al., *Validation of DSM-5 age-of-onset criterion of attention deficit/hyperactivity disorder (ADHD) in adults: Comparison of life quality, functional impairment, and family function.* Res Dev Disabil, 2015. **47**: p. 48-60.
16. Dalsgaard, S., et al., *Mortality in children, adolescents, and adults with attention deficit hyperactivity disorder: a nationwide cohort study.* Lancet, 2015. **385**(9983): p. 2190-6.
17. Konofal, E., M. Lecendreux, and S. Cortese, *Sleep and ADHD.* Sleep Med, 2010. **11**(7): p. 652-8.
18. Huang, Y.S. et al., *Sleep disorders in Taiwanese children with attention deficit/hyperactivity disorder.* J Sleep Res, 2004. **13**(3): p. 269-77.
19. Allen, et al., *Validation of the self-completed Cambridge-Hopkins questionnaire (CH-RLSq) for ascertainment of restless legs syndrome (RLS) in a population survey.* Sleep Med, 2009. **10**(10): p. 1097-100.
20. Allen, Bharmal, and Calloway, *Prevalence and disease burden of primary restless legs syndrome: results of a general population survey in the United States.* Mov Disord, 2011. **26**(1): p. 114-20.
21. Walters, et al., *Review of Severity Rating Scales for Restless Legs Syndrome: Critique and Recommendations.* Mov Disord Clin Pract, 2014. **1**: p. 317-324.
22. Kessler, R.C., et al., *The World Health Organization Adult ADHD Self-Report Scale (ASRS): a short screening scale for use in the general population.* Psychol Med, 2005. **35**(2): p. 245-56.
23. Adler, L.A., et al., *Validity of pilot Adult ADHD Self- Report Scale (ASRS) to Rate Adult ADHD symptoms.* Ann Clin Psychiatry, 2006. **18**(3): p. 145-8.
24. Kessler, R.C., et al., *Validity of the World Health Organization Adult ADHD Self-Report Scale (ASRS) Screener in a representative sample of health plan members.* Int J Methods Psychiatr Res, 2007. **16**(2): p. 52-65.
25. Kim, J.H., E.H. Lee, and Y.S. Joung, *The WHO Adult ADHD Self-Report Scale: Reliability and Validity of the Korean Version.* Psychiatry Investig, 2013. **10**(1): p. 41-6.
26. Sonnby, K., et al., *Validation of the World Health Organization Adult ADHD Self-Report Scale for adolescents.* Nord J Psychiatry, 2015. **69**(3): p. 216-23.

27. Poulsen, L., et al., *[Danish standardization of the attention deficit hyperactivity disorder rating scale]*. Ugeskr Laeger, 2009. **171**(18): p. 1500-4.
28. Hines, J.L., T.S. King, and W.J. Curry, *The adult ADHD self-report scale for screening for adult attention deficit-hyperactivity disorder (ADHD).* J Am Board Fam Med, 2012. **25**(6): p. 847-53.
29. Rigas, A.S., et al., *Predictors of iron levels in 14,737 Danish blood donors: results from the Danish Blood Donor Study.* Transfusion, 2014. **54**(3 Pt 2): p. 789-96.
30. Pedersen, C.B., *The Danish civil registration system.* Scandinavian journal of public health, 2011. **39**(7 suppl): p. 22-25.
31. Batool-Anwar, S., et al., *Lifestyle Factors and Risk of Restless Legs Syndrome: Prospective Cohort Study.* J Clin Sleep Med, 2016. **12**(2): p. 187-94.
32. Szentkiralyi, A., et al., *Socio-economic risk factors for incident restless legs syndrome in the general population.* J Sleep Res, 2012. **21**(5): p. 561-8.
33. Virring, A., et al., *Disturbed sleep in attention-deficit hyperactivity disorder (ADHD) is not a question of psychiatric comorbidity or ADHD presentation.* J Sleep Res, 2016. **25**(3): p. 333-40.
34. Gao, X., et al., *RLS in middle aged women and attention deficit/hyperactivity disorder in their offspring.* Sleep Med, 2011. **12**(1): p. 89-91.
35. Oner, P., et al., *Association between low serum ferritin and restless legs syndrome in patients with attention deficit hyperactivity disorder.* Tohoku J Exp Med, 2007. **213**(3): p. 269-76.
36. Steinlechner, S., et al., *Restless legs syndrome as a possible predictor for psychiatric disorders in parents of children with ADHD.* Eur Arch Psychiatry Clin Neurosci, 2011. **261**(4): p. 285-91.
37. Wagner, M.L., A.S. Walters, and B.C. Fisher, *Symptoms of attention-deficit/hyperactivity disorder in adults with restless legs syndrome.* Sleep, 2004. **27**(8): p. 1499-504.
38. England, S.J., et al., *L-Dopa improves Restless Legs Syndrome and periodic limb movements in sleep but not Attention-Deficit-Hyperactivity Disorder in a double-blind trial in children.* Sleep Med, 2011. **12**(5): p. 471-7.
39. Ferri, R., et al., *Time structure of leg movement activity during sleep in attention-deficit/hyperactivity disorder and effects of levodopa.* Sleep Med, 2013. **14**(4): p. 359-66.
40. Hvolby, A., *Associations of sleep disturbance with ADHD: implications for treatment.* Atten Defic Hyperact Disord, 2015. **7**(1): p. 1-18.
41. Ullum, H., et al., *Blood donation and blood donor mortality after adjustment for a healthy donor effect.* Transfusion, 2015. **55**(10): p. 2479-85.
42. Thireau, J., et al., *MEIS1 variant as a determinant of autonomic imbalance in Restless Legs Syndrome.* Sci Rep, 2017. **7**: p. 46620.
43. Moro, M., et al., *Periodic limb movements of sleep: empirical and theoretical evidence supporting objective at-home monitoring.* Nat Sci Sleep, 2016. **8**: p. 277-89.

Table 1. Demographic and clinical features of the study population

Characteristics	RLS N=1,322	No RLS symptoms N=24,014	P *
Involuntary leg movements during sleep (%)	22.3	-	-
Female sex (%)	57.6	45.0	<.001
Age (mean ±SD)	42.2 (12.3)	41.3 (12.7)	0.006
Body mass index (Mean ±SD)	25.8 (4.2)	25.7 (4.1)	0.419
Smoker (%)	15.5	13.0	0.007
Frequent alcohol consumption (%)	38.3	35.5	0.042
Whole blood donation frequency for the past three years (mean ±SD)	5.2 (2.5)	5.4 (2.6)	0.004
Poor quality of sleep (%)	10.1	4.6	<.001
ADHD symptoms			
ASRS score (Mean ±SD)	23.0 (8.3)	19.4 (7.8)	<.001
Full ASRS scale (score>36 on all 18 questions) (%)	5.7	2.4	<.001
Screening version of ASRS (score>6 on questions 1-6) (%)	4.2	2.0	<.001
Inattentive subtype (score ≥24 on questions 1-4 and 7-11) (%)	1.4	0.7	0.003
Hyperactivity-impulsivity subtype (score ≥24 on questions 5-6 and 12-18) (%)	1.4	0.5	<.001

*Body mass index was transformed using square root to obtain normal distribution before examining significant differences between RLS and non-RLS sufferers.

Table 2. Univariate and multivariate linear regression analyses with Restless Legs Syndrome (RLS) as the independent variable and continuous ASRS score as the dependent variable

Non-RLS cases, n=24,014 RLS cases, n=1,322	Univariable analyses Coef. (95 % CI)	P	Model 1* Coef. (95 % CI)	P	Model 2** Coef. (95 % CI)	P
Comparison groups: RLS vs. no RLS						
Full ASRS scale (score on all 18 questions)	3.56 (3.13-3.99)	<.001	3.57 (3.14-4.00)	<.001	3.26 (2.84-3.68)	<.001
The full scale divided into the ADHD subtypes						
Inattentive subtype (score on questions 1-4 and 7-11)	1.61 (1.37-1.86)	<.001	1.66 (1.43-1.90)	<.001	1.52 (1.28-1.75)	<.001
Hyperactivity-impulsivity subtype (score on questions 5-6 and 12-18)	1.95 (1.70-2.19)	<.001	1.90 (1.66-2.14)	<.001	1.74 (1.50-1.98)	<.001

*Adjusted for sex, age, body mass index (BMI), alcohol consumption, smoking status, and whole blood donation frequency for the past three years

**Adjusted for sex, age, BMI, alcohol consumption, smoking status, and whole blood donation frequency for the past three years and quality of sleep (poor/good)

Table 3. Univariate and multivariate logistic regression analyses with restless legs syndrome (RLS) as the independent variable and ADHD symptoms as the dependent variable

Non-RLS cases, n=24,014 RLS cases, n=1,322	**Univariable analyses**		**Model 1***		**Model 2****	
	OR (95 % CI)	P	OR (95 % CI)	P	OR (95 % CI)	P
Comparison groups: RLS vs. no RLS						
ADHD symptoms						
Full ASRS scale (score≥37 on all 18 questions)	2.44 (1.90-3.12)	<.001	2.62 (2.04-3.37)	<.001	2.34 (1.81-3.03)	<.001
Screening version of ASRS (score≥14 on the first 6 questions)	2.22 (1.67-2.95)	<.001	2.51 (1.88-3.35)	<.001	2.27 (1.69-3.04)	<.001
The full scale divided into the ADHD subtypes						
Inattentive subtype (score ≥24 on questions 1-4 and 7-11)	2.05 (1.25-3.34)	0.004	2.25 (1.37-3.68)	0.001	1.91 (1.15-3.15)	0.012
Hyperactivity-impulsivity subtype (score ≥24 on questions 5-6 and 12-18)	2.81 (1.73-4.57)	<.001	4.28 (2.55-7.18)	<.001	3.46 (2.04-5.89)	<.001

*Adjusted for sex, age, body mass index, alcohol consumption, smoking status, and whole blood donation frequency for the past three years

**Adjusted for sex, age, body mass index, alcohol consumption, smoking status, and whole blood donation frequency for the past three years and quality of sleep (poor/good)

Table 4. Univariate and multivariate logistic regression analyses with restless legs syndrome (RLS) as the independent variable and ADHD symptoms as the dependent variable

Non-RLS cases, n=24,109 RLS cases with ILMS, n=295	**Univariable analyses**		**Model 1***		**Model 2****	
	OR (95 % CI)	P	OR (95 % CI)	P	OR (95 % CI)	P
Comparison groups: RLS cases with involuntary leg movements during sleep (ILMS) vs. RLS cases without ILMS (N=295/1,027)						
ADHD symptoms						
Full ASRS scale (score≥37)	1.91 (1.36-2.68)	<.001	2.15 (1.30-3.55)	0.003	2.04 (1.22-3.41)	0.007
Screening version of ASRS (score≥14)	2.36 (1.35-4.09)	0.002	2.12 (1.21-3.74)	0.009	2.00 (1.13-3.56)	0.018
The full scale divided into the ADHD subtypes						
Inattentive subtype (score ≥24 on questions 1-4 and 7-11)	2.83 (1.11-7.25)	0.030	2.54 (0.97-6.68)	0.058	2.17 (0.80-5.88)	0.126
Hyperactivity-impulsivity subtype (score ≥24 on questions 5-6 and 12-18)	6.18 (2.41-15.84)	<.001	5.57 (2.14-14.5)	<.001	5.24 (1.98-13.9)	0.001
Comparison groups: RLS cases with involuntary leg movements during sleep (ILMS) vs. non-RLS cases (N=295/24,014)						
ADHD symptoms						
Full ASRS scale (score≥37)	4.25 (2.86-6.33)	<.001	4.33 (2.88-6.51)	<.001	3.69 (2.42-5.61)	<.001
Screening version of ASRS (score≥14)	4.05 (2.60-6.31)	<.001	4.24 (2.69-6.69)	<.001	3.62 (2.26-5.78)	<.001
The full scale divided into the ADHD subtypes						
Inattentive subtype (score ≥24 on questions 1-4 and 7-11)	4.13 (2.01-8.48)	<.001	4.28 (2.07-8.86)	<.001	3.42 (1.63-7.20)	<.01
Hyperactivity-impulsivity subtype (score ≥24 on questions 5-6 and 12-18)	8.17 (4.47-14.95)	<.001	8.09 (4.39-14.91)	<.001	6.61 (3.54-12.37)	<.001

*Adjusted for sex, age, body mass index, alcohol consumption, smoking status, and whole blood donation frequency for the past three years

**Adjusted for sex, age, body mass index, alcohol consumption, smoking status, and whole blood donation frequency for the past three years and quality of sleep (poor/good)

Highlights

- Individuals with restless leg syndrome (RLS) have an increased risk of attention-deficit-hyperactivity-disorder (ADHD)
- RLS sufferers with involuntary leg movements during sleep are more prone to experience ADHD symptoms compared to sufferers without ILMS
- Quality of sleep explains the association only to a limited extent
- RLS and ADHD may be comorbid disorders